Effects of Intensive Lifestyle Intervention on All-Cause Mortality in Older Adults With Type 2 Diabetes and Overweight/Obesity: Results From the Look AHEAD Study

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OBJECTIVE

Look AHEAD, a randomized trial comparing intensive lifestyle intervention (ILI) and diabetes support and education (DSE) (control) in 5,145 individuals with overweight/obesity and type 2 diabetes, found no significant differences in all-cause or cardiovascular mortality or morbidity during 9.6 (median) years of intervention. Participants in ILI who lost ≥10% at 1 year had lower risk of composite cardiovascular outcomes relative to DSE. Since effects of ILI may take many years to emerge, we conducted intent-to-treat analyses comparing mortality in ILI over 16.7 years (9.6 years of intervention and then observation) to DSE. In a secondary exploratory analysis, we compared mortality by magnitude of weight loss in ILI relative to DSE.

RESEARCH DESIGN AND METHODS

Primary outcome was all-cause mortality from randomization to 16.7 years. Other outcomes included cause-specific mortality, interactions by subgroups (age, sex, race/ethnicity, and cardiovascular disease history), and an exploratory analysis by magnitude of weight loss in ILI versus DSE as reference. Analyses used proportional hazards regression and likelihood ratio.

RESULTS

The incidence of all-cause mortality did not differ significantly in ILI and DSE (549 and 589 participants, respectively) (hazard ratio [HR] 0.91 [95% CI 0.81, 1.02]; $P = 0.11$). There were no significant differences between treatments in cause-specific mortality or within prespecified subgroups. ILI participants who lost ≥10% at 1 year had a 21% reduced risk of mortality (HR 0.79 [95% CI 0.67, 0.94]; $P = 0.007$) relative to DSE.

CONCLUSIONS

ILI focused on weight loss did not significantly affect mortality risk. However, ILI participants who lost ≥10% had reduced mortality relative to DSE.

Individuals with type 2 diabetes have a higher risk of all-cause mortality than those without diabetes. Although diabetes-related risk has decreased over time, excess

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**Members of the Look AHEAD Research Group Writing Committee are listed in the APPENDIX. A complete list of the members of the Look AHEAD Research Group can be found in the supplementary material online.*

mortality risk associated with diabetes is ~6 deaths/1,000 person-years (with ~2 deaths/1,000 due to cardiovascular disease [CVD] and a significantly elevated risk for at least 9 major causes) (1). A meta-analysis found that the intensive medical management of glucose did not improve mortality among persons with type 2 diabetes (2), and, in the ACCORD trial, intensive glucose management by pharmacologic therapy increased mortality (3). This raises the important question of whether a lifestyle intervention can reduce mortality in individuals with overweight/obesity and type 2 diabetes.

Although unintentional weight loss is associated with increased mortality, especially in older individuals (4–6), intensive lifestyle intervention (ILI) focused on producing intentional weight loss may have positive effects on mortality through changes in eating patterns, physical activity, and/or improvements in cardiovascular risk factors (7–9). Two meta-analyses (10,11) of randomized controlled trials suggest possible beneficial effects of lifestyle weight loss interventions on all-cause mortality. However, the studies in these analyses often had small sample sizes (except the initial data from Look AHEAD) and short follow-up intervals; the CI for the effects on mortality were large and included 1.0.

Look AHEAD provides a unique opportunity to examine the long-term effects of an intensive lifestyle intervention focused on weight loss in individuals with type 2 diabetes. Look AHEAD was a randomized trial of ILI compared with diabetes support and education (DSE) (control) in 5,145 individuals with overweight/obesity and type 2 diabetes (12). The Look AHEAD intervention was stopped after a median follow-up of 9.6 years because there was no evidence that ILI reduced cardiovascular morbidity or mortality relative to DSE (13); however, the study has continued to observe these participants over time, with new primary aims for this phase of the study, one of which is to test the hypothesis that the rates of all-cause mortality over a median of 16.7 years of follow-up (from randomization) will be reduced in ILI versus DSE. This hypothesis is based on the fact that ILI, relative to DSE, had larger weight losses, greater improvement in cardiovascular fitness, and positive effects on a large number of risk indicators for all-cause mortality, including HbA_{1c}, depression, systolic blood pressure, renal function, gait speed, and fitness levels (13,14). Although for many of these measures the differences between ILI and DSE were greatest in year 1 of the intervention, in prior randomized trials, there has been evidence of "legacy effects" or "metabolic memory," in which initial changes in weight or glycemic control continue to have positive effects on outcomes even after the initial differences have diminished (15,16). Moreover, in the Da Qing Study, it took 30 years of follow-up to show positive effects of lifestyle intervention on CVD and all-cause mortality in individuals with impaired glucose tolerance (17); thus, longer follow-up is warranted.

Although the primary aim of this manuscript is to present an intent-to-treat analysis comparing ILI and DSE on mortality, we also report a secondary analysis comparing participants who had different magnitudes of weight loss at year 1 in ILI relative to DSE on mortality over the extended follow-up interval. This secondary aim is based on extensive prior data showing that a 10% weight loss produces clinically significant health benefits (18). In addition, a prior report from Look AHEAD showed that participants who lost ≥10% of their weight at 1 year had a 21% lower risk of the primary composite cardiovascular outcomes (including both fatal and nonfatal heart attacks and strokes and hospitalized angina) between years 2 and the end of the intervention relative to those who were weight stable or gained (19). Since 92% of the participants who achieved the 10% weight loss goal were in ILI, similar results (20% lower risk) were seen when those who achieved this weight loss in ILI were compared with DSE as the reference group. Using the latter approach, we have extended the comparison of participants in ILI who achieved different magnitudes of weight loss to the DSE group, now focusing on all-cause mortality and considering the full 16.7 years.

RESEARCH DESIGN AND METHODS

Study Design

Look AHEAD was conducted at 16 clinical sites in the U.S.; all analyses were completed by the coordinating center. The institutional review board at each of these sites approved the study. The study was sponsored by the National Institutes of Health (NIH), with additional support from other federal partners. Detailed descriptions of the study design, including the full list of eligibility criteria and detailed descriptions of the interventions and all assessments, have been published previously (12,20,21), and the full protocol is available online (https://www.lookaheadtrial.org).

Participants were recruited between 2001 and 2004 and randomly assigned to either ILI or DSE, with stratification by clinic site. The intervention was stopped in September 2012, when the median follow-up was 9.6 years. At that time, a decision was made to continue Look AHEAD as an observational study, with additional follow-up extending to July 2020.

The Look AHEAD Extension (Look AHEAD-E) had its own primary and secondary aims, separate from those of the original randomized trial. A primary aim of Look AHEAD-E was to examine whether random assignment to ILI relative to DSE reduced all-cause mortality rates over a median follow-up of 16.7 years in adults with type 2 diabetes and overweight/obesity. We also examined cause-specific mortality, mortality during the intervention and postintervention phases separately, and in prespecified subgroups. Finally, we present a post hoc observational analysis of the relationship between magnitude of weight loss during the 1st year of ILI, relative to all DSE participants, and subsequent all-cause mortality risk.

Participants

A total of 5,145 participants were randomly assigned into the trial. Basic eligibility criteria included 45–76 years of age, type 2 diabetes, BMI ≥25 kg/m^2 (≥27 kg/m^2 if taking insulin), blood pressure <160/100 mmHg, HbA_{1c} ≤11%, triglycerides <600 mg/dL, able to complete a valid maximal exercise test, and an established relationship with a primary care provider. Additional eligibility criteria are available in prior publications and in the protocol. Participants randomly assigned to ILI (N = 2,570) and DSE (N = 2,575) were similar at baseline (see Supplementary Table 1 for baseline characteristics of ILI and DSE) (22,23). A total of 436 deaths occurred during the intervention phase of the study (2001–2012), and 4,316 of the

4,709 living participants (92%) consented to participate in the postintervention observational phase with similar percentage of participants retained in ILI versus DSE and no differences in their baseline characteristics.

Interventions

Participants were randomly assigned to ILI or DSE. The interventions have been described in detail previously (21,22). The goal of the ILI intervention was to produce at least a mean 7% weight loss through a combination of decreased calorie intake (goal of 1,200–1,800 kcal/day) and increased physical activity (goal of 175 min/week of moderate-intensity activity). Participants were given an individual goal of losing ≥10% of baseline weight to facilitate achievement of the studywide goal. Participants attended a combination of group and individual sessions weekly for 6 months, with gradually decreasing frequency of contact thereafter. Behavioral strategies, including self-monitoring and goal setting, were emphasized throughout the program. The DSE group was invited to three to four group meetings each year, focused on education about diet, exercise, or social support, without individualized plans or feedback.

Assessments

Participants attended clinic visits at baseline, annually during the intervention period, and every 2 years during the postintervention follow-up. At each visit, weight was assessed with a digital scale, and blood pressure was measured. Questionnaires and fasting blood work were completed at selected visits. More detail is available in the protocol (https://www.lookaheadtrial.org).

Outcomes

Mortality was adjudicated by a physician committee masked to intervention assignment. Adjudicators evaluated death certificates, hospitalization records, informant interviews with relatives, and a National Death Index search. All deaths reported from randomization through 30 June 2020 were included. Time to death from any cause was measured from the time of randomization. All 5,145 participants had at least a partial observation and thus were used in the survival analysis. Specific cause of death was available for 89% of the deaths and was categorized as cancer, cardiovascular, and other.

Statistical Analyses

The primary analysis for all-cause mortality was an intent-to-treat analysis using proportional hazards regression with stratification for clinical sites. Follow-up time was calculated as the time in years from randomization to their last available visit or to their death. Significance for the intervention effect was based on the likelihood ratio test. Hazard ratio (HR) and 95% CIs were constructed from the fitted models, and Kaplan-Meier plots were used to present the survival curves by intervention. A simulation-based P value for adequacy of the proportional hazard's assumption was 0.14, meaning that the modeling assumption of proportionality was satisfied (24).

Subsequent analyses examined whether the hazard rates differed during the intervention compared with the postintervention phases of the trial and cause-specific mortality (cardiovascular, cancer, and other). Tests of interactions were done to assess the consistency of differences between intervention groups for each of the prespecified subgroups (sex, history of CVD, and race/ethnicity). Age was entered as a continuous variable with HRs for the point estimates for the first and third quartiles. P values were adjusted using the Hommel method (25).

Secondary Analyses

As an exploratory post hoc analysis, we also examined differences in mortality for post hoc subgroups defined by their initial weight loss during year 1 of the intervention relative to the full DSE group. These analyses paralleled an approach reported previously for the cardiovascular outcomes of Look AHEAD and are akin to a per-protocol or on-treatment analysis (19). Using the same categories as used previously (20), participants in ILI were divided into subgroups based on their weight loss from baseline to 1 year (≥10% weight loss, ≥5 to <10% weight loss, ≥2 to <5% weight loss, and <2% loss or weight gain), and the risk of mortality subsequent to 1 year (i.e., starting at year 2) for each subgroup was computed relative to the risk of mortality in the DSE group as a whole. This analysis was done adjusting for baseline factors that varied across the weight change groups: age, sex, diabetes duration, insulin use, history of CVD, smoking status, weight, LDL cholesterol, and blood pressure.

Statistical Power

Because total mortality was monitored over time, we prespecified a final critical value for testing the intervention effect of 2.6, corresponding to a nominal P value of 0.01, instead of 1.96 (i.e., the common unadjusted two-sided $\alpha = 0.05$). Given the assumption of 509 deaths in DSE by July 2020 and a loss to follow-up of <1%/year, we had 88% power to detect a difference between the two arms if the intervention effect was 20% during Look AHEAD-E.

RESULTS

Weight Loss Outcomes

As reported previously (22), the ILI produced significantly greater initial weight loss than DSE, with mean percent weight losses of 8.6% in ILI compared with 0.7% in DSE at year 1 (<0.001), 6.0% versus 3.5% at the end of intervention ($P <$ 0.001), and 8.6% in ILI and 7.5% in DSE ($P = 0.013$) at the median 16.7-year visit. At 1 year, 38% of ILI participants had lost ≥10% of their body weight.

All-Cause Mortality Risk in ILI Versus DSE

Over the median 16.7 years of follow-up, there were 549 deaths among the 2,570 participants randomly assigned to ILI (21.0%) and 589 among the 2,575 in DSE (23.0%). The HR for total mortality was 0.91 (95% CI 0.81, 1.02; $P = 0.11$) for ILI versus DSE (Fig. 1). We also examined the effect on mortality during the period of the active intervention (through September 2012) and subsequently. The HR during the period of the intervention was 0.86 (0.70, 1.05), and the HR in the postintervention period was 0.94 (0.81, 1.08). The interaction between intervention and time period was not significant ($P = 0.47$) (Supplementary Fig. 1).

Cause-Specific Mortality

Specific causes of death ($N = 1,138$) also did not differ by treatment arm ($P =$ 0.27) (Table 1). The primary cause of death was adjudicated as cancer in 334 cases (177 in DSE and 157 in ILI); cardiovascular in 303 cases (149 in DSE and 154 in ILI), and other in 379 cases (207 in DSE and 172 in ILI). The three most

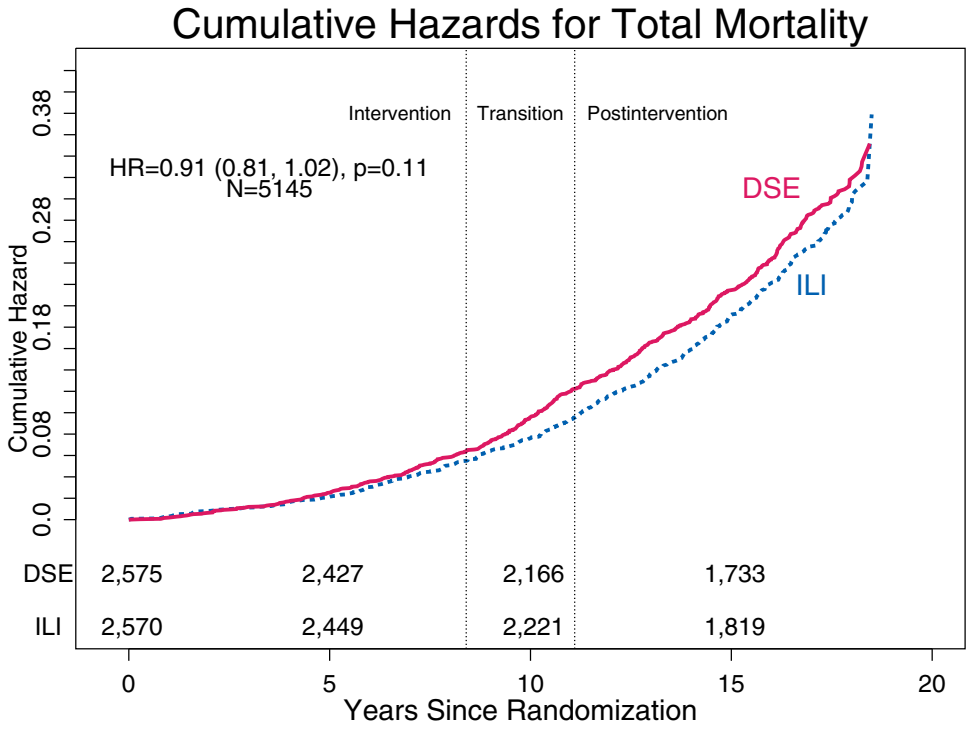

Figure 1—Cumulative hazards for total mortality in ILI and DSE.

common other causes of death were infectious (46 in DSE and 44 in ILI), neurological (30 in DSE and 29 in ILI), and pulmonary (26 in DSE and 18 in ILI) diseases. The specific cause of death was unknown in 122 cases (56 in DSE and 66 in ILI).

Subgroup Analyses

We found no evidence of significant interactions between treatment and any of the following demographic variables: sex, age, race/ethnicity, or history of prior CVD (Fig. 2). As expected, there were main effects of each of these variables on mortality.

Secondary Post Hoc Analysis

In an observational post hoc analysis (Table 2), we found a significant interaction between magnitude of weight loss during the 1st year of the ILI intervention and risk of all-cause mortality relative to the DSE group as the reference ($P = 0.02$). Comparing ILI participants with different magnitudes of initial weight loss, we found that ILI participants who lost ≥10% of their body weight in the 1st year of intervention had a 20% reduced risk (HR 0.80 [CI 0.67, 0.94]; $P = 0.007$) during years 2 to the end of the Look AHEAD-E phase of the trial relative to all participants in DSE; the effect on mortality appeared to be related to the magnitude of weight loss, with a nonsignificant trend for participants in ILI who gained weight or lost <2% to be at increased risk (HR 1.19 [CI 0.94, 1.50]; $P = 0.15$).

Table 1—Cause of death in the ILI and DSE ($P = 0.27$ for overall difference between ILI and DSE)

Causes of death	DSE	ILI	Total
Cancer	177 (30)	157 (29)	334
Cardiovascular	149 (25)	154 (28)	303
Other	207 (35)	172 (31)	379
Accidental	21	20	41
Complications of diabetes	3	2	5
Gastrointestinal	7	2	9
Hepatobiliary/pancreas	22	9	31
Infectious	46	44	90
Neurological[1]	30	29	59
Other known cause	4	7	11
Pulmonary	26	18	44
Renal failure	12	12	24
Unclassifiable	36	29	65
Unknown	56 (10)	66 (12)	122
Total	589	549	1,138

Data are *N* (%) unless otherwise indicated. [1]Neurological causes of death include Parkinson disease, dementia, and other neurologic diseases.

CONCLUSIONS

Look AHEAD is the largest, longest randomized trial of ILI focused on weight loss in adults with overweight/obesity and type 2 diabetes. We found a 9% reduction in total mortality for ILI relative to DSE, but this difference was not statistically significant. The nominal 99% CI, which accounts for the history of sequential testing during intervention, includes effects between a reduction of 22% and an increase of 6%. Thus, randomization to ILI neither

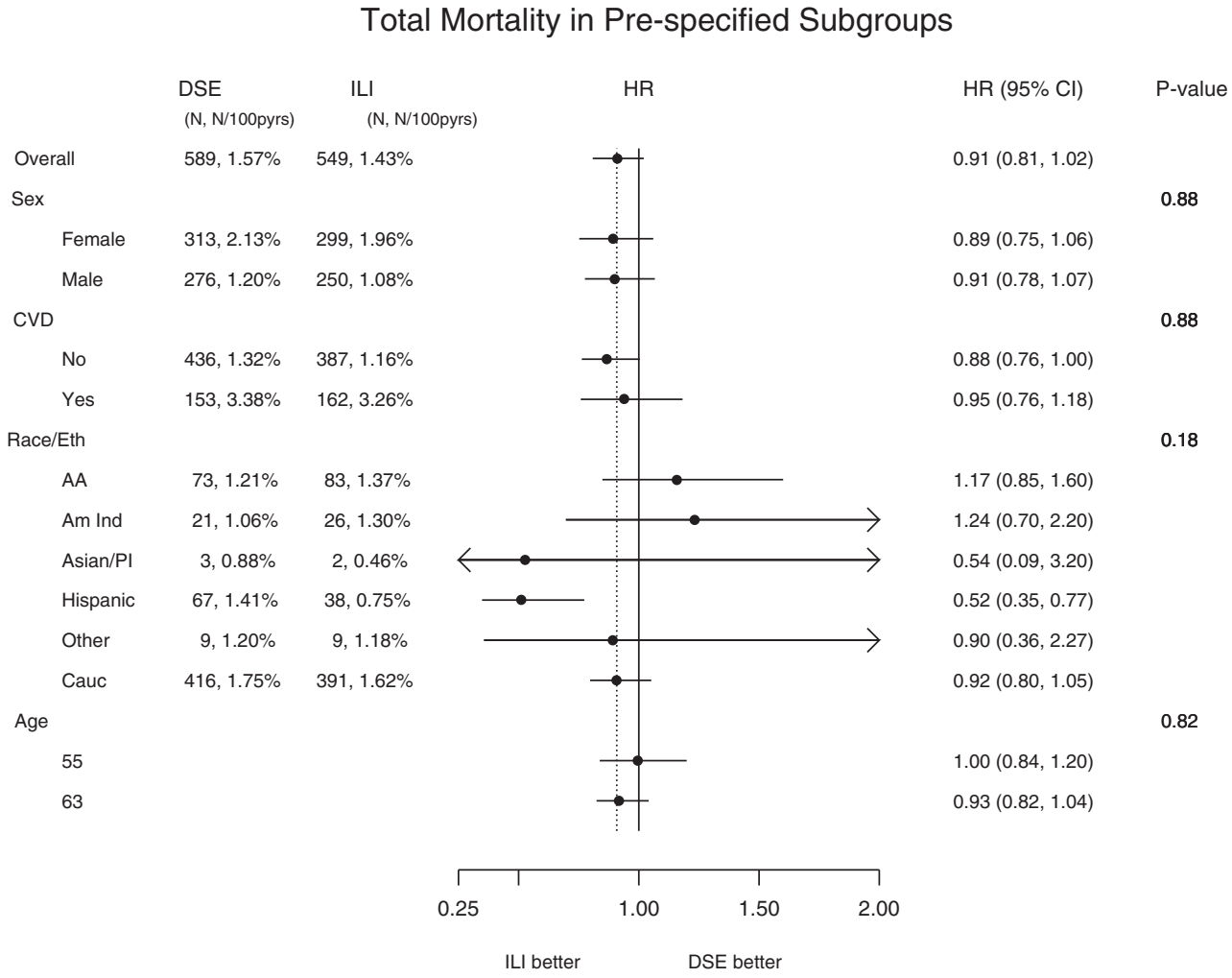

Figure 2—Total mortality in prespecified subgroups. Age was entered as a continuous variable, and HRs are for the point estimates for the first and third quartiles. Dashed line shows overall HR. AA, African American; Am Ind, American Indian; Cauc, Caucasian; Eth, ethnicity; PI, Pacific Islander; pyrs, person-years.

significantly reduced nor increased risk of mortality relative to DSE.

At the outset of the Look AHEAD Extension, there were several reasons to hypothesize that the lifestyle intervention would reduce all-cause mortality. First, ILI had a significant effect on body weight throughout the study. The Arthritis, Diet, and Activity Promotion Trial (ADAPT) had shown small long-term effects on mortality with weight losses and duration of follow-up that were similar in magnitude to those found in Look AHEAD (26). Secondly, as reported in prior publications (13,14,27,28), the lifestyle intervention had beneficial effects on risk factors for mortality, including glycemic control and diabetes remission, fitness, disability, systolic blood pressure, gait speed, and renal function. Collectively, these changes were hypothesized to result in reductions in all-cause mortality in Look AHEAD. Although for many of these measures, the differences between ILI and DSE were greatest at year 1 and diminished over time (22), these changes could still affect mortality through "metabolic memory" or "legacy effects." However, our results did not support this hypothesis, and there were no significant differences in mortality for ILI and DSE.

The lack of difference between intervention and control group in all-cause mortality is consonant with the data presented recently from the Diabetes

Table 2—HR for all-cause mortality for 1-year weight change categories in ILI vs. all DSE[1] (*P* = 0.02 for overall difference)

ILI weight change categories vs. DSE	*N*	*N* deaths	*P* value	HR	95% CI
≥10% loss in ILI	934	197	0.007	0.79	0.67, 0.94
≥5 to <10% loss in ILI	750	150	0.241	0.90	0.74, 1.08
≥2 to <5% loss in ILI	433	92	0.531	0.93	0.74, 1.17
<2% loss or gain in ILI	358	82	0.153	1.19	0.94, 1.52

[1]Model included a variable with four categories for weight change in ILI and one category for all of DSE. Other covariates included age, sex, history of CVD, insulin use, weight, diabetes duration, LDL, systolic and diastolic blood pressure, smoking history, race/ethnicity, and stratification by clinic.

Prevention Program (DPP) (29) and previously in Look AHEAD (22). Likewise, these results confirm our earlier finding of no significant differences between treatment arms in the specific causes of death and the percentage of deaths attributable to cardiovascular causes (27% in the present analysis and 29% at the end of the intervention). The interactions between treatment and subgroups were also not significant. Although there seemed to be a beneficial effect of lifestyle intervention among Hispanic individuals, this finding is limited by the clustering of Hispanic participants within a few clinics, the relatively small number of events in these participants, and the lack of significance of the overall interaction effect for treatment × race/ethnicity. However, this finding deserves further investigation.

The failure to find significant differences between arms in all-cause mortality may have resulted from characteristics of the cohort (e.g., their age or degree of obesity) (30). Although we had previously suggested that the lack of an effect on mortality in Look AHEAD might have resulted from the participants' long duration of diabetes, the similarity of the results from DPP suggests that this is not likely to be the explanation (29). The decreases over time in the differences between ILI and DSE for changes in weight, HbA_{1c}, and other CVD risk factors could also have contributed (22). Greater use of statins and hypertensive medications in DSE relative to ILI (22) may also have blunted any beneficial effect of intervention. In addition, the lack of differences in risk of mortality between arms could have resulted from the decreased incidence in all-cause mortality and cardiovascular mortality in particular, among adults with diabetes in the U.S. and other countries (1,31). All-cause death rates in adults with diabetes in the U.S. have declined from 23.1 in 1988–94 to 15.2/1,000 person-years currently, and the causes of death shifted from primarily CVD to other causes. In Look AHEAD, we found that only 27% of deaths were from cardiovascular causes (29% from cancer, 33% from other, and 11% unknown). The decrease in cardiovascular deaths may reflect better treatment of CVD risk factors (32). Since power estimates for Look AHEAD were based on earlier studies, these temporal trends may have affected our power to detect differences between the treatment arms (33). Moreover, given these trends, future studies should pay greater attention to "other" causes of mortality (including infectious, pulmonary, and renal diseases).

Our analyses showed no significant beneficial effects of intensive lifestyle intervention on mortality, but, conversely, we found no negative effects. Epidemiological studies frequently suggest associations between weight loss and subsequent mortality, especially in older populations, but this likely results from the association between unintentional weight loss and more severe disease or unrecognized health problems (4–6). A meta-analysis (11) suggested an excess risk of mortality of 22–39% associated with unintentional weight loss and a small benefit of intentional weight loss for individuals classified as unhealthy (with obesity-related risk factors) (relative risk 0.87 [95% CI 0.77, 0.99]; $P = 0.028$). Given the difficulty of distinguishing unintentional and intentional weight loss (typically done by post hoc self-report), Look AHEAD used a randomized trial design in which participants were randomly assigned to ILI focused on weight loss or to DSE. Since participants in ILI were provided goals and treatment structure to achieve the prescribed weight loss, weight loss in ILI is assumed to be intentional. Although this type of randomized design is the best way to distinguish intentional versus unintentional weight loss, some participants in DSE may have lost weight intentionally, and some in ILI lost weight unintentionally, especially in the later years of the trial (34). Moreover, since ILI sought to achieve weight loss through a low-calorie, lower-fat diet and increased physical activity, it is possible that these behavior changes were related to health outcomes.

Our exploratory analysis of the relationship between 1-year weight loss and subsequent mortality, although post hoc with clear limitations, suggests that the magnitude of weight loss a participant achieved during the 1st year of ILI was associated with subsequent mortality risk relative to the control group. Those participants who lost $\geq$10% of their initial body weight during the 1st year of ILI had significant reductions in mortality relative to the control group, whereas those who lost $<$2% or gained weight during the 1st year of ILI had a nonsignificant increase in mortality.

Several points should be considered in interpreting these findings. First, the magnitude of weight loss was related to mortality risk, but only the group of ILI participants who had a 10% weight loss at 1 year had significant reductions in risk of mortality; this magnitude of weight loss was achieved by $<$40% of the ILI group. However, even more modest weight losses have also been shown to improve many other health outcomes, including outcomes of great importance to patients and physicians (18,35). The difference in mortality in this observational analysis may relate not only to the magnitude of weight loss per se, but also to the fact that the ILI program led to improvements in CVD risk factors, fitness, gait speed, and lower incidence of high-risk kidney disease relative to DSE (13,14,27,28). Using an observational approach similar to the current secondary analysis, our previous publication found that lifestyle participants with a 10% weight loss at year 1 had a 20% reduction in the primary composite cardiovascular outcome of the original Look AHEAD trial during the intervention compared with DSE as the reference group (19). Likewise, those participants in ILI who had the greatest improvements in fitness at 1 year (19) had significant reductions in the primary outcome relative to the control. Maintenance of weight loss (vs. initial weight loss) may also affect long-term outcomes, but we did not examine this. Finally, the differences in mortality in this observational analysis may relate to baseline differences between ILI participants who achieved larger weight losses and those who lost less or gained weight. Differences in adherence to ILI are related to weight loss (36), and there are positive effects of good adherence on mortality (37).

This study has its strengths and limitations. The Look AHEAD study had a large sample size, excellent retention, sustained differences in weight loss, and a long period of observation. There was sufficient power to detect a mortality difference of 20%. Limitations include the fact that findings from the Look AHEAD population are not generalizable to all persons with diabetes, as participants in the trial were required to have a source of medical care, successfully complete a maximal treadmill test for study entry, and be willing to join a

randomized trial. We used a low-calorie, low-fat diet prescription and did not compare differences due to the macronutrient composition or to level of adherence to the diet. The PREDIMED study (38), which randomly assigned participants to diets high in olive oil or nuts or to a control, found positive effects on cardiovascular but not all-cause mortality. Look AHEAD focused on weight loss rather than changes in body composition, which may also affect long-term health outcomes. Since body composition was measured with DXA only on a subset of participants, we were not powered to assess the association with mortality. As noted above, there are limitations in interpreting findings related to our exploratory analysis of magnitude of weight loss and risk of mortality, as this is inherently an observational analysis of participants who did not adhere to the original intention-to-treat. Finally, it remains unknown whether a trial using a more intensive weight loss program that could produce greater weight losses (e.g., a behavioral intervention augmented with pharmacologic treatment), even longer follow-up, or a study population with less morbidity at baseline would yield different outcomes.

In conclusion, Look AHEAD found no statistically significant difference in all-cause mortality over a median of 16.7 years of follow-up in ILI compared with control. There was some evidence that those in ILI who lost ≥10% of their body weight at 1 year had lower subsequent mortality. Although lifestyle intervention did not significantly decrease risk of mortality, it did not increase risk of mortality in this older population, as is often seen with unintentional weight loss. In a prior analysis using statistical modeling with Look AHEAD results during the intervention period, Gregg et al. (39) found that ILI did not affect the total number of years of life but did have a significant positive effect on healthy life years. Thus, clinicians should be reassured about recommending that adults with type 2 diabetes with overweight or obesity participate in intensive lifestyle programs focused on weight loss. However, such recommendations should be based on the beneficial effects of intensive lifestyle intervention on a variety of physical and psychological outcomes and on quality of life, not on expectations of lower mortality risk.

APPENDIX

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Author Contributions. R.R.W. wrote the manuscript. D.M.R. conducted the analyses. D.M.R. and L.E.W. had access to all of the data. R.R.W., J.M.C., C.E.L., F.X.P.-S., and T.A.W. were principal investigators of sites and responsible for study conduct at their sites. All authors reviewed the manuscript and contributed to this final version. The Look AHEAD Publications and Presentation Committee and the Steering Committee approved the decision to submit for publication. D.M.R. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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